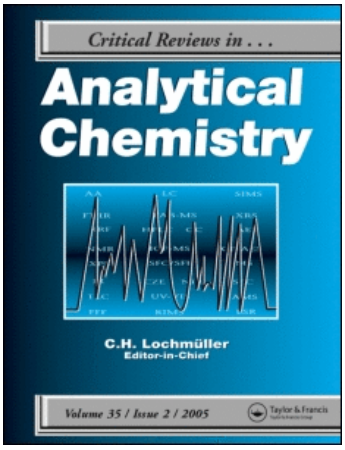

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Electrochemical Sensor Arrays

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ABSTRACT: The importance of sensor arrays in environmental, food and clinical analysis is discussed. The possible designs of sensor arrays is shown. The most reliable mathematical models for data processing are presented. The importance of different types of electrochemical sensor arrays in analytical chemistry as well as their performances are shown.

KEY WORDS: sensor arrays, design, chemometrics.

I. INTRODUCTION

Due to the possibility to measure direct, without any prior separation the activity of species in solutions, electrochemical sensors can assure the best results for the analysis of components in different matrices. These electrochemical sensors are used in each branch of analytical chemistry: environmental analysis, food analysis, and clinical analysis. Electrochemical sensors arrays provide the highest precision, especially when they are used in clinical analysis. Simultaneous analysis of components became increasingly important in the last few years. This could be achieved by the utilization of electrochemical sensors for simultaneous detection in array. As a result, the analysis with sensor arrays became competitive with quantitative chromatographic analysis techniques. Sensor arrays are preferred over chromatographic techniques because no laborious sampling processes (e.g., extraction, derivatization) are required; the separation itself is not so reproducible, the chromatographic techniques need high-quality materials (e.g., solvents, inert gases) and are time consuming.

Fabrizion et al.[1] defined the following main topics for sensor arrays: design, calibration, and deconvolution. The design of sensor array plays a very important role in the quality of the analytical information, especially when used for *in vivo* measurements in clinical analysis.[2] High-quality standards are requested for the calibration of sensor arrays. Also, a sufficiently large number of measurements on known samples is necessary[1].

Data processing was proven to have the minimum uncertainty value, especially when an artificial neural network method is used,[3] because methods for characterization of the electrodes and statistical tools for processing the raw data are vitally important in array research. Special instrumentation with certain software for data recording is required for sensor array utilization.[4] The lack in this kind of instrumentation made the development of sensor array's introduction into electrochemical sensor research very slow.

The utilization of sensor array as detection systems in flow analysis increases the objectivity and rapidity of analysis.[2, 5-7] It was shown that consideration of cell design both in terms of geometry and the associated potentiostatic control is important in the construction of sensor arrays;[6] the wall-jet cell was proven to be a useful geometry for this purpose. The developments in the construction of electrochemical sensor arrays made it possible to obtain a chemical fingerprint of complex matrices.[8,9]

The main types of electrochemical sensors utilized in the construction of sensor arrays are ion-selective, membrane electrodes, amperometric sensors, gas sensors, ISFET, piezoelectric sensors, and biosensors. Despite their importance in clinical analysis and their high selectivity, immunosensors are not yet used very often for sensor array construction.[10] The importance of microelectrodes array and electronic noses increased in the last few years, mainly due to their utilization for *in vivo* measurements. Their development makes possible to consider them, separately, as main classes of sensor arrays.

II. THE DESIGN OF THE ELECTROCHEMICAL SENSOR ARRAYS

The design of sensor array has to take into account its field of utilization: clinical analysis, process analytical chemistry, alloys analysis, environmental analysis, food analysis, etc. The first characteristic considered for the design of sensor arrays is its matrix compatibility with the medium where it has to be used. The geometry and size must be selected in concordance with the purpose of sensor array construction. The design of sensor array is a result of the research in a team. Usually, the main persons in this team are the analyst who can select the best matrix and active materials and the electronist who is able to make the sensor in concordance with options of the analyst. Despite their low reproducibility in construction, the polymer-based matrices are preferred to carbon paste-based matrices for sensors design.

Very often, the sensor arrays contain ion-selective, membrane electrodes, gas sensors, and biosensors. There are sensor arrays that contain different types of sensors, for example, for analysis of blood a sensor array based on two gas sensors (pO_2, pCO_2) and on the ion-selective, membrane electrode (pH sensor) as working electrodes is proposed.[11] The sensor array is an integrated silicon chip containing five chemically sensitive Si_3N_4 gate FETs(O_2, CO_2 and pH-sensitive electrodes, reference, and pseudo-reference electrodes).

A. Tin Oxide-Based Sensor Arrays

For the determination of odours,[12] H_2S, and NO_2[13] in complex matrices, the transient characteristics of tin oxide sensors were considered. Three kinds of sensors were used for sensor arrays construction: SnO_2, SnO_2-Pt, and SnO_2-Pd. The increase in measurement error with increasing calibration error was counter-balanced by adding an auxiliary sensor to the array.

B. Silicon-Based Sensor Arrays

A sensor array was designed by integrating eight thin film metal oxide sensors on a silicon substrate.[14] Their sensitivity should be improved with thin film sensors. The purpose of this is multicomponent analysis for process analytical chemistry, and it was proposed for the simultaneous assay of acetone and methanol. This design based on silicon improved the quality of the same sensor array based on bulk ceramic.

C. Metal-Based Sensor Arrays

An array based on platinum-on-copper electrodes is proposed.[6] They are prepared

using double-side copper-clad glass fiber electronic circuit board (2 mm thick). The design was drawn using a printed circuit board computer-aided design package (Board Maker V 1.31) with through-hole plating to enable a connection on the reverse side of the face supporting the electrode array. The copper electrodes produced were plated with 25 μm of gold by an in-house printed circuit board production facility. The gold layer allowed electrodeposition of a platinum surface. A platinum layer was also electrodeposited. The through-hole plating was blocked using epoxy resin potting compound, and the electrodes were polished back to a flat surface using 1 mm Dialap paste.

D. Electronic Noses Design

Holmberg et al.[15] proposed two methods for countering drift in an electronic sensor array. The first is a self-organizing classifier that stores the patterns of the different gas responses. The second designs the sensor as a dynamic system. The sensor array consists of 15 gas sensors, 10 of which were metal oxide semiconductor field effect transducer (MOSFET) with different gates made of different catalyst metals of different thickness and operated at different temperatures to provide selectivity.

E. Polymer-Based Sensor Arrays

Due to the possibility to be used in clinical analysis for *in vivo* measurements, a microsensor array design was adopted most of the time. The combinatorial polymer synthesis and also the derivatization procedures for polyvinylchloride (PVC) made it possible to obtain a high variety of polymers. Polymerization reactions between different combinations of two starting materials have been found to lead to many new, unique sensors with responses not simply related to the proportion of the starting materials.[16] This approach is demonstrated in two ways: (1) the use of discrete polymer sensing cones each comprised of a specific monomer combination, and (2) the fabrication of a gradient sensor, containing all combinations between the starting and ending monomer concentrations.

Cosofret et al.[17] and Lindner et al.[18] conducted studies concerning the bio-compatibility of derivatized PVC matrices used for microsensor arrays construction. They connected the biocompatibility of the matrix with the response characteristics of sensors as well as with their selectivity. It was proven that also the type and ratio of plasticizer in the matrix play an important role in both electrode response and biocompatibility of the sensor. As a result, a minimum quantity of plasticizer must be used. The utilization of carboxylated PVC in the ratio 1:1 with the plasticizer for microsensor arrays construction assure the best biocompatibility, and the sensor responses and selectivity are close or similar with the sensors having a matrix with classic composition, that is, 1:2 polymer to plasticizer ratio.[17]

Microlithographic techniques are used for microelectrode arrays construction. Polymers films can be deposited at the microelectrode arrays using anodic galvanostatic current densities.[19] Redox polymer-based sensor arrays are also described. The design of the arrays is based on the incorporation of a metal — that is able to change electrons — in a derivatized polymer, for example, Os(II)/Os(III) redox couple is reported for Fe(III) assay using the {Os(2,2′-bipyridyl)2[poly(4-vinylpyridine)]10Cl}Cl polymer films crosslinked with 10% 1,10-dibromodecane.[20]

A biosensor array based on conductive polymer/enzyme coated is proposed for glucose, penicillin, and pH simultaneous assay.[21] Ultra-thin conductive polymers hydrophobically pre-treated are used for enzymes immobilization. The main disadvantage of this construction type is nonuni-

formity and nonreproducibility of enzyme repartition into the polymer matrix.

F. Glassy Carbon-Based Sensor Arrays

Glassy carbon-based sensor arrays have got the most reproducible construction. For their design Fielden et al.[6] reported the following: the glassy carbon discs are polished to give a flat surface using silicon carbide abrasive paper in a succession of finer grades (120 to 1000 grade). Further polishing was achieved by first polishing with a 1 μm Dialap paste, and then by three polishing procedures using graded alumina (0.3, 0.075, and 0.015 μm, respectively) in a water-based slurry. Once a mirror finish had been achieved, the electrodes were joined together electrically, and the whole array was electrochemically pretreated by applying an initial potential of +1.3 V (vs Ag/AgCl) for 5 min., followed by a final potential of -0.6V (vs. Ag/AgCl) for a further 5 min. Electrodes were not repolished unless significant deactivation was observed. Regular electrochemical cleaning between experiments was found to prolong the working period after polishing.

III. CHEMOMETRICS FOR ELECTROCHEMICAL SENSOR ARRAYS

In the last few years chemometrics became increasingly important for all analytical methods. Chemometrics is already not only a science but also an art. The status of art is given by the best chosen between mathematical models for data processing. Data processing for sensor arrays cannot be done without chemometrics, especially when the selectivity of the sensors is not good enough. Therefore, chemometrics is considered the key for sensor arrays development.

When used in array, the selectivity of individual sensors is not of fundamental importance. Sensors should not only be sensitive enough for the maximum number of components determined (having high cross-sensitivity), but also differ in the parameters associated with the sensitivity.

When applied to chemical analysis, pattern recognition is divided into three steps: extraction of characteristic features, classification, and identification. The extraction of features is an algorithm of preprocessing of the response of a sensor array and consists in extraction of quantitative data from the response.

Due to the modification that can appear in sensor response when it is a part of sensor arrays, a high importance must be allocated to sensor signal preprocessing. In this regard, improvements for instruments construction[22,23] and for equations that defined the sensor response[24] were recorded. The design and operation of collective analogue circuitry was used to process the outputs from an array of chemical sensors in order to permit robust chemical discrimination.[22]

The dimensions and geometries of sensor arrays influences their responses. A new equation for current intensity was proposed for this type of sensors.[24] Except for interdigitated arrays, an ideal, convection-independent, response behavior can be achieved only for microelectrode arrays that have an extremely low current efficiency when compared with macroelectrodes of similar size. Also, for signal preprocessing some mathematical models[25,26] were given in place of a new equation that defined a potential or a current.

Classification represents the separation of classes from responses of a sensor array. Essentially, classification is calibration. The neural network is one of the best mathematical models that can be used for sensor arrays calibration.[27] For gas sensor arrays, lifelong calibration method represents a good alternative for pattern recognition techniques.[28]

Forster and Diamond[29] proposed a nonlinear calibration of ion-selective electrode arrays for flow injection analysis.

Identification is the assignment of a given pattern (responses of a sensor array) to a certain class. It represents the treatment of data obtained in measuring samples of unknown composition. The modeling techniques are classified in: parametric modeling procedures (e.g., partial least squares [PLS], non-linear partial least squares [NPLS]), and nonparametric modeling procedures (e.g., multivariate adaptive regression splines, projection pursuit regression). The most used modeling techniques are multilinear regression (MLR),[30] PLS,[30-33] non-linear partial least squares (NPLS),[32,33] artificial neural networks (ANN),[30,32,34,35] principal component analysis (PCA),[26,36] multivariate analysis of variance (MANOVA),[26,37,38] fuzzy neural networks,[39] linear discriminant analysis (LDFA).[26]

ANN was found superior to MLR, PLS, and NPLS.[30,32,34] The maximum error can be obtained when MLR is used; the best results can be recorded through this mathematical model for the small interferences. PCA assures better results for gas sensor arrays. LDFA has got a disadvantage: there is no allowance for overlapping of class models; the data do not need to be standardized prior to analysis as it is the case with PCA. Generally, it was proven that non-parametric techniques are superior to parametric techniques. The best modeling technique was found to be the multivariate adaptive regression splines.[33]

To improve the quality and reliability of data processing, the following tandem modeling techniques have been proposed: feedforward neural network was used in tandem with the resilient back-propagation (RPROP) learning algorithm,[31] fuzzy clustering algorithm was used in tandem with a radical basic function neural network,[40] itineration techniques were used in tandem with the multiple regression method for the identification of mixtures of gases using an integrated gas sensor array.[41]

Tandem modeling techniques improve recognition and classification compared with modeling techniques alone and gave information about classes. The best performance was obtained because of correlation of the samples and the total characteristics of the classes.

IV. ELECTROCHEMICAL SENSOR ARRAYS TYPES

Usually, electrochemical sensor arrays contain electrochemical sensors of the same type. It is therefore easy to classify the electrochemical sensor arrays in ion-selective electrode arrays, gas sensor arrays, ISFET arrays, piezoelectric sensor arrays, and biosensor arrays. A special class of sensor arrays is electronic noses. To be able to use sensor arrays for *in vivo* measurements, they must be miniaturized, to give the microelectrode arrays type. The construction of the sensor arrays using different types of electrodes of different sensitivities will permit a simultaneous detection of minor and major components of the matrix.

A. Ion-Selective Eclectrode Arrays

The main fields of the utilization for ion-selective electrode array are environmental analysis and clinical analysis. A sensor array formed by clacogemide glass electrodes was used for quantitative analysis of solutions.[42,43] A sensor array based on Orion-type electrodes for the simultaneous calcium and fluoride assay is recommended for the determination of these ions in water samples.[44]

For the determination of mercury, silver, chloride, bromide, and iodide in aquatic systems, an ion-selective electrode array based on Hg and Ag graphite composite type sensors is recommended.[45] The response of the Hg sensor was linear for the 1 pmol/l to 0.1 mol/l concentration range, although the response was greater for 0.1 to 10 nmol/l Hg(II)

in solutions of $HgCl_2$ than for the higher and lower ranges of Hg(II) present in $HgBr_2$ and mercury (II) nitrate, respectively. The response for Ag(I) was linear for the 1 pmol/l to 0.1 mol/l concentration range. Fe(II) and Fe(III) caused significant interferences and must be removed.

In clinical analysis it is important to determine the concentration of K^+, Na^+, and Ca^{2+} ions as well as the pH. In this regard ion-selective electrode arrays for simultaneous analysis are reported.[46,47] The electrodes used for the array assembly are designed by combining film and coated wire electrodes.[46] Response times for preconditioned electrodes applying a commercial reference system were of a few seconds magnitude order; using an integrated miniature reference electrode response times were ~ 15 s. Detection limits were 5 μmol/l K^+, 10 μmol/l Na^+, 0.3 nmol/l H^+, and 0.5 μmol/l Ca^{2+}. The corresponding linear ranges were 10 μmol/l to 0.1 mol/l, 20 μmol/l to 0.5 mol/l, 1 nmol/l to 0.01 mol/l, and 5 μmol/l to 0.02 mol/l, respectively.

B. Gas Sensor Arrays

Walmsley et al.[48] show a methodology for the selection of suitable sensors for incorporation into a gas sensor array taking into account the influence of gas sensors onto each other when they are in array. Resistance characteristics of conducting polymer films must be taken into account for polymer based gas sensor arrays construction.[49]

To improve the response characteristics, an analogue signal processing technique is proposed.[50] The output signal of the sensor array was sampled at various intervals to produce wavefronts with characteristics patterns that allowed the analyte to be distinguished. The approach reduced the overall response time, for example, when applied for CO monitoring, the response time was reduced from 10 to 2 s.

The main important application field for gas sensor arrays is for environmental analysis: air composition determination. The compounds analyzed can be of the inorganic[51] and/or organic[52] type.

An amperometric-type gas sensor array is proposed for nitrogen oxides discrimination.[53] Simultaneous detection of H_2S and NO,[54] as well as of CO and CH_4,[55] can be done using a gas sensor array based on SnO_2; for data processing ANN is proposed. The SnO_2-based gas sensor arrays are also very often used for volatile organic compounds assay.[56,57]

Four commercially available Taguchi gas sensors are proposed for simultaneous determination of ethanol, toluene, and *o*-xylene in the 25 to 100 ppm concentration range.[58] For continuous and simultaneous assay of hydrocarbons, nitrogen oxides, and O_2, a gas sensor array consisting of potentiometric and amperometric devices based on zirconia is proposed.[59] The detection of oxidizing and reducing gases in combustion atmospheres can be done easily using a 16 sensing elements sensor array, on an alumina substrate formed by tin oxide thin layers.[60] Benzene, toluene, methanol, acetone, and trichloroethylene can be assayed simultaneously at ppm concentration level using an array packed on a silicon chip wafer (3×3 mm) based on reactively sputtered single- and bi-layers of SnO_2, ZnO, and WO_3.[61]

The reliability of analytical information obtained for simultaneous analysis of gases and/or volatile compounds in air using gas sensor arrays made them suitable for on-line simultaneous detection.[62] Gas sensor arrays can be utilized for food quality assay by determination of aromas[63] and freshness of food through its odor.[64]

The quality of wine is given by the aromas that it contains. By using a metal oxide-based gas sensor array[65] for aromas assay in wine, the reliability of analytical information increases. The proposed technique is superior to standard chemical analysis; more

information is obtained that enable a more accurate classification.

A multilayer conducting polymer gas sensor array is proposed for aroma determination in brandies;[66] gin and spirits can be distinguish through aroma composition assay by using this type of sensor. The determination of liquor aromas can be done using a six semiconductor gas sensor array.[67] The application of cluster analysis resulted in the classification of eight alcoholic beverages.

A CO, H_2S, CO_2, and NO amperometric sensor array, a heated catalyst, and a data evaluation were used successfully to detect volatile organic compounds (alcohols, carbonyl compounds, amines, sulfides and thiols) that show the freshness of the fish.[68] The flavor compounds in food can be reliably detected using a gas sensor array based on SnO_2 at a ppm concentration level.[69,70]

An array of five miniature Clark-type oxygen electrodes was fabricated on a glass substrate (26 mm × 7 mm) by thin film technology.[71] The array was coated by an outer silicone membrane. Cyclic voltammetric studies showed that the device exhibited a good response to dissolved oxygen. Sensor arrays for biochemical oxygen demand were prepared by immobilizing the yeast *Trichosporon cutaneum* onto the cathode of the oxygen electrode. It can be used successfully for biochemical oxygen assay.

C. Ion-Selective Field Effect Transitors (ISFET) Arrays

A sensor array for analyzing hydrogen and ammonia gas mixtures in humid air has been developed, built into a rugged system, and calibrated for laboratory testing.[72] The sensor array is comprised of four chemically sensitive field-effect transistors (CHEMFETs). The sensor array showed good sensitivity, selectivity, response time, and stability and is recommended for field deployment.

For pH measurements, a very large integrated pH-ISFET sensor array is recommended.[73] Measurement accuracies are in the range 99.8 to 99.9%.

D. Piezoelectric Sensor Arrays

Response kinetics of chemically modified quartz piezoelectric crystals during odorant stimulation was studied using crystals coated with either pyridoxine hydrochloride, Antarox CO-880, pyridoxinehydrochloride/Antarox CO-880, ascorbic acid, or OV-17.[74] The odorants used were a group of related amines, a group of related acetates, and several others. By precise control of the odorant concentration and its duration, and also by precise control of odorant flow rate, characteristic time-dependent frequency responses were observed for each odorant–surface interaction. The time-dependent responses were repeatable for each sensor and reproducible among sensors and were less variable than the maximum frequency response. This study permits the best selection of sensor arrays for simultaneous assay of sample components.

For piezoelectric sensor array characterization, equations describing sensitivity, signal-to-noise ratio, selectivity, and limit of detection are applied to quartz micro-balance and surface acoustic wave devices.[75] These equations identify parameters that affect performances. Two quartz micro-balance arrays with seven sensors are compared for both seven-analyte and three-analyte systems. The coefficients of variance are several times reduced from the seven- to the three-analyte system for the array selected by principal components analysis. Crown ethers-coated piezoelectric crystal sensor array is recommended for organic vapour mixture assay.[32]

Piezoelectric sensors have got a high sensitivity, but they are losing the selectivity. They can easily be used for environmen-

tal analysis, for classification of organic compounds in groups, because most of them have only group selectivity, for example, a piezoelectric sensor array is proposed for simultaneous classification of organic compounds from environmental samples into alcoholic, carbonyl, etherous, and esterous group.[76]

Nakamura et al.[77] proposed a piezoelectric sensor array coated with a plasma polymer film for simultaneous determination of benzene, acetone, and methanol. Hierlemann et al.[78] and Auge et al.[79] also described polymer-based piezoelectric sensor arrays for simultaneous detection of organic vapors in the environment.

Some stationary phases used in chromatography, for example, OV1, OV-275 (Supelco), ASI-50 (Applied Science Laboratories Inc.),[80] SE-54, DC-170, and OV-225,[81] are proposed as selectors for piezoelectric arrays designs. These arrays can be used successfully for the simultaneous analysis of organic substances in the environment. For organic substances analysis at ppm level in sea water, a piezoelectric array based on gold electrodes is proposed.[82]

A piezoelectric crystal sensor was used for simultaneous assay of two or three components in a liquid by observing the kinetic adsorbtion process onto a synthetic multibilayer lipid membrane that was coated on both sides of the piezoelectric crystal sensor.[83]

Food freshness can also be detected by using a piezoelectric sensor array.[84] Various metalloporphyrins were evaluated as coating materials for piezoelectric sensors. The quality of alcoholic and nonalcoholic beverages was determined using a piezoelectric sensor array for alcohols vapors discrimination.[85]

A microprocessor controlled sensor system consisting on piezoelectric sensors was developed that could be adjusted to identify complex odors.[86] The system could be applied for quality control in the food and cosmetics industries, for the detection of smoldering fires, and from the signal patterns obtained for the differentiation of species.

A piezoelectric quartz sensor array with nonselective but different sensitive coating materials was used to analyze anaesthetics gases.[87] Pattern recognition techniques were used to handle the sensor signals. By applying this method, it was possible to identify different volatile fluorinated anesthetics such as halothane, enflurane, isoflurane, and seroflurane. Substances that are often used in GC techniques as stationary phases were used for the coating of piezoelectric sensors design. Using this piezoelectric sensor array in coupling with pattern recognition method will increase the number of gases that can be identified with the array.

E. Biosensor Arrays

The main application of biosensor arrays in analytical chemistry is clinical analysis. Therefore, they must be constructed using biocompatible materials in view of *in vivo* measurements.

The transducer sensitivity can be considered the key for a reliable analysis using biosensor arrays. The most suitable transducer for biosensors are amperometric ones. Zhu et al.[88] characterized from an electrochemical point of view the hydrogen peroxide microarray electrodes as base elements for biosensors design. Two geometrical forms were tested for microelectrodes in band and in square of silicon wafers. The sensor contains Pt counter-electrodes and Ag/AgCl reference electrodes. The performances of 12 different types were tested with a solution of 1 mmol/l $K_3[Fe(CN)_6]$ in 0.1 mol/l KCl. The best results for sensitivity and response time were obtained with an array of 225 squares, each 10 μm. Calibration graphs were linear for 0.01 to 1 mmol/l $K_3[Fe(CN)_6]$ solution with a slope of 277 nA/ mmol/l and a RSD of 1.8%. This sensor was used to determine H_2O_2 in 70 mmol/l phosphate buffer of pH 7,

with the current measured at + 0.7 V. Calibration graphs were linear for 0.1 to 5 mmol/l H_2O_2 solution concentrations, with a mean slope of 550 nA/ mol/l and a RSD between five sensors of 16.1%. The sensor was coated with glucose oxidase and used to determine glucose via the H_2O_2 obtained in the enzymatic reaction. The sensitivity of the array was tenfold greater than a single microelectrode.

Penicillin can be determined with a detection limit of 0.5 μmol/l using a biosensor with a pH-sensitive microarray electrode as transducer.[89] The pH-sensitive microarray electrode was coated with polypyrrole and penicillinase membranes. The enzyme reaction acidifies the polypyrrole membrane, resulting in an increase in the electrical conductivity of polypyrrole that is then measured.

Of great importance is the developing of a biosensor array for determination of glucose in blood streams. A biosensor array based on polyaniline is proposed for the simultaneous assay of glucose, urea, and lipids.[90] Layers of Cr (~ 20 nm) and Au (1 μm), deposited sequentially on 100 p-type Si (5 Ω cm) with a 100 nm oxide film, were etched to give a single substrate sensor. Glucose oxidase, triacylglycerol lipase, and ureas were immobilized on the sensor from array. Experimental data showed excellent agreement with a line of unit slope derived from a plot of sensor response vs. actual concentration. Enzyme microelectrode array strips are reported for glucose and lactate simultaneous assay.[91] Carbon microdisk arrays were treated to incorporate enzymes and to produce disposable amperometric test strips for glucose and lactate. The 15-μm-diameter pores in the strips were used for the codeposition of glucose oxidase or lactate oxidase and Rh or Pt, which was achieved by placing 200-μl drops of solution containing 100 ppm of metal, enzyme, and 0.03 mol/l NaCl on the strip. The preferential catalytic action of Rh particles toward the oxidation of the liberated H_2O_2 gave selective monitoring of the glucose substrate and eliminated the need for membrane barriers. The detection limits recorded are of μmol/l magnitude order.

A miniaturized liquid handling system comprising a thin film biosensor array is described for rapid liver enzyme assay.[92] The miniaturized analysis system ($42 \times 22 \times 1.5$ mm) was based on the detection of the glutamate produced as a result of transaminase activity, using a thin film glutamate biosensor array. The sensor array (4×7 mm^2) comprised two active, two inactive sensors (no glutamate oxidase), and a Ag/AgCl reference electrode. Calibration graphs were linear for up to 200 iu/l enzyme. The activity range covered both normal and pathological state enzyme concentrations.

The utilization of biosensors for environmental analysis have not achieved good results due to the low selectivity assured by enzyme; sometimes, the maximum selectivity obtained is group selectivity. A biosensor array based on microband array Au electrodes (Micro Sensor Systems, Kentucky, USA) is proposed for the assay of phenol vapors.[93] The determination of metals (e.g., Cd, Cr) and organic pollutants (e.g., atrazine, phenol, pentachlorophenol) in potable water[94] can be done successfully through a six-enzyme sensor array. Nonspecific enzyme inhibitors are feasible in detecting pollutants. None of the models giving false-negative and false-positive rates were acceptable. The method should be useful for raw water monitoring and for drinking water production. It will lead to the development of disposable biosensor arrays for continuous monitoring.

The reliability of analytical information obtained by using the biosensor arrays made them suitable for flow systems. A microdialysis sampling interface a small scale in extracorporeal shunt circuit forms the main part of a miniaturized Total Chemical Analysis System for on-line determination of glucose and lactate in core blood plasma of

dogs.[95] A silicon-machined microflow manifold and integrated biosensor array, with enzymic sensor based on glucose oxidase and lactate oxidase, are also included. The system is under computer control. Blood flow was maintained at 3 ml/min. Results are reported for lactate and glucose in blood plasma; however, the results obtained for lactate assay were less reliable than those for glucose assay.

A mass producible miniaturized flow through — a device with a biosensor array is proposed for assay of glucose and lactate.[96] This is based on a thin film device consisting of four Pt working electrodes (0.5 mm × 0.5 mm) and a Ag/AgCl reference electrode on a glass carrier (0.3 mm thickness). The working electrodes were covered with a semipermeable membrane of poly(1,30 diaminobenzene) onto which glucose oxidase or lactate oxidase were immobilized in a photochemically cross-linked pHEMA membrane and subsequentially covered with a diffusion limiting layer that contained catalase. Biosensors responses were measured at 500 mV vs Ag/AgCl electrode at pH = 7.4 and a flow rate of 50 µl/min. Calibration graphs were linear for up to 40 mmol/l for glucose and 25 mmol/l for lactate, respectively.

F. Electronic Noses

"Electronic nose is an instrument that comprises an array of electronic chemical sensors with partial specificity and an appropriate pattern recognition system, capable of recognizing simple or complex odours".[97] This definition restricts the term electronic nose to those types of intelligent chemical array sensor system or chemical sensoric array devices (ChemSADs) that are used specifically to sense odorant molecules in an analogue to the human nose.

The most commonly reported application is their use to classify the smell (or flavor) of various beverages or food. In some cases this simply grades the samples and in other tests is used for freshness. Besides the assessment of various food and beverages, there is considerable scope in the field of environmental analysis. Odor control is of increasing importance in our lives, for example, in automobiles, trains, aircraft, inside and outside of buildings and factories. It is quite likely that there will be increasing interest in the use of electronic noses in the medical field. One particularly exciting prospect is the use of an electronic nose to supply diagnostic information to medical practitioners. The Chinese have used smell for thousands of years to help diagnose. Classic examples are acetone on the breath of diabetics, halitosis for stress or stomach disorders, and a sweet skin smell for Hanse's disease.

General similarities may be seen already between the natural chemosensory systems and the electronic noses. The specific recognition site on a certain transducer is the key component of the total sensor system. A large amount of different materials with different recognition sites can be already utilized today for a chemical and biochemical sensor system.[98,99] The most successful electronic noses are based on modular sensor systems, for example, sensor system in which different transducers are used whereby each transducer principle is applied to several sensor elements. This leads to a maximum "orthogonality" in the determination of independent chemical or odor information.

The design of bioelectronic noses that utilize biological function units is evidently more complex. Usually their stabilities are limited and hence time-dependent signal outputs cause serious problems in calibration procedures. Significant progress is recorded by screening systematically new materials with stabilized biological functions. For bioelectronic nose, the weakest component is the sensor itself, including the transducer; piezoelectric and multielectrode sensor arrays assure the best sensitivities. The development of the bioelectronic noses is driven by the curiosity to obtain a basic sci-

ence understanding of structural and functional aspects of natural chemosensory systems, the need to monitor parameters that represent more directly impressions of human odor sensations, and the need for designing hybrid systems in order to make optimum use of similarities and differences between technical and biological chemosensory systems/[99]

Despite the growing number of applications, much development work is still required before electronic noses can reach their full potential. There are a number of limitations to current commercial instruments, including the high cost, large size, and weight, humidity and temperature dependence, sensor poisoning, poor reproducibility and repeatability, high power consumption, relatively low sensitivity, long response times and even longer recovery periods (up to several minutes), long-term drift and instability, and interference from other gases.[100] They remain a simplified simulation of their biological counterparts. The advances in artificial olfaction will continue to be influenced by future investigations into the mechanisms of the natural olfactory system in terms of noise reduction, signal amplification, and improved pattern recognition algorithms.

Electronic noses technology based on gas sensor array combined with multivariate data processing methods as artificial neural network has been demonstrated to have a promising potential for rapid nondestructive analysis of odor and flavor in foods. It may be applicable in quality control of raw material, food processing, or products.[101]

As with all new techniques, some basic problems remain to be solved concerning sample handling and instrumental performance. The emerging research activity in the development of chemical sensors, including hardware and software combined with this technique will be implemented online in the food industry in the near future. In particular, promising applications on meat seem to be within the field of spoilage, off-flavor, sensory analysis, and fermentation processes. The freshness evaluation, shelf-life investigation, and authenticity assesments for meat, grains coffee, mushrooms, cheese, sugar, fish, beer, as well as for odor quality evaluation of food packaging material were done using an electronic nose.[102]

An array of 10 MOSFET sensors with different catalytic metal gates, four commercial SnO_2 chemical sensors, and a CO_2 sensor is proposed for freshly ground beef and pork determination.[103] It determined the type of sample (beef or pork) as well as the storage time.

The determination of food aroma compounds is essential for the quality control of food. Electronic nose based on conducting polymer sensors designed by electrochemical growth of sensor materials (polymer, counter ion, solvent) onto working electrodes are proposed for food aroma compounds assays.[104,105]

For beer, cola, and stored cereals, the system comprises a measurement chamber for generation of the odor and a detection system consisting of a sensor array containing 6, 12, or 18 sensors.[106] The results from the sensor array are then collected to form an odor fingerprint. The sensor array is made up with metal oxide sensors or a combination of metal oxide sensors and conducting polymers. For the determination of beer quality, an electronic nose was constructed with up to 12 conducting polymer sensors, each with a partial sensitivity to headspace species from beer.[107] The electronic nose can show differences between commercial beers and, notably, between standard and artificially brewed beers.

A microprocessor controlled device that was developed to mimic the human sense of smell is recommended for tobacco odor, alcohol, and beer odor discrimination.[108] It consists of an array of solid-state chemical gas sensors with associated signal processing and pattern recognition systems.

Tan et al.[109] described an electronic nose capable of detecting simple and complex odors for discrimination of different types of

coffee, cola, and sausages. The electronic nose comprises an array of nonselective gas sensors including metal oxide sensors and conducting polymers. Odorous samples were heated in a glass container, the vapors were extracted, and drawn over the sensors by a carrier gas at 50 to 500 ml/min. Data were processed using neural networks.

An electronic nose containing sensors coated with GC stationary phases was used for spices assay.[110] The electronic nose can give results equivalent to those of the human nose, but with the advantage of objectivity. Eklov et al.[111] recently reported an electronic nose to monitor a sausage fermentation in order to follow the changes in emitted volatile compounds during the fermentation process and to compare the electronic nose results with a sensory analysis.

Monitoring lot-to-lot variation in bioprocess medium ingredients, detecting microbial contamination early, and evaluating bioprocess performance during cultivation of microorganisms at inoculum and production stages can be done successfully using an electronic nose.[112] Given the considerable time and expense invested in a single bioprocess (fermentation) batch, variability and loses must be identified quickly. The proposed electronic nose is based on conductive polymer membrane sensors.

A new method for distinguishing pollen from other airborne particulates is based on utilization of an electronic nose.[113] Three types of pollen, diesel, and petrol soot, and dust from windows adjacent to traffic and soil, were analyzed. The electronic nose comprised nine metal oxide semiconductor FET with Pt, Ir, and Pd gates operated at 140 and 170°C. Using neural network for data processing, it was possible to distinguish between the different types of pollen.

A semiconductor electronic nose containing 15 elements has been designed to detect various volatile organic compounds at ppm concentration magnitude order.[114] The main components of the array have been titanium oxide and tin oxide semiconductors oxides with different thicknesses. Good response times, sensitivity, and reproducibility values have been obtained. The utilization of titanium oxide for sensors preparation increases the selectivity of electronic nose.

G. Microelectrode Arrays

The most important field for microelectrode arrays is *in vivo* simultaneous analysis of inorganic and/or organic compounds. Clinical analysis needs high precision. For this reason, it is important to make a reliable evaluation of the microelectrode arrays. The most suitable techniques for characterization and evaluation of microsensor arrays are surface analysis techniques.[115, 116] For microelectrode arrays based on a combination of screen printing and laser ablation, scanning electrochemical microscopy provides a straightforward test demonstrated that all array elements participate in the heterogeneous redox reaction.

The evaluation of gold and platinum ultrathin ring microelectrodes (0.1 to 0.5 mm thick, 1.5 to 4 mm diameter) used in a thick layer wall jet flow cell demonstrate that all the electrodes possessed rugged mechanical stability (except for sputtered metal rings) and could be resurfaced repeadtedly as required.[117] Acceptable temporal stability was observed with gold microelectrodes made by thinly coating borosilicate glass with gold metallorganic paint, by the vapor deposition of gold onto glass, and by gluing gold foil onto glass. Of these, the thin gold paint electrodes have the best signal-to-noise properties and are rivaled only by a jet-centered carbon microdisk electrode with respect to low background signal.

The standards used for the calibration of an microelectrode array and data processing are of the same importance.[118] The role of standards and reference materials increase when the microelectrode array must be used

for *in vivo* measurements. There are only a few standards and reference materials available for clinical analysis.[119]

Amperometric sensors are the most suitable sensors for clinical analysis because of their high sensitivity. Therefore, they are very often used in microsensor arrays design for *in vivo* measurements.

The microelectrode array based on Clark-type sensors can be used for O_2 and H_2O_2 detection. It can replace the traditional macroelectrodes. Furthermore, it can be used as a subsensor for over 100 different biosensors using oxygenases (enzymes). These sensors show the greater benefit of being independent of the sample flow rate or stirring.[120]

A microelectrode array with 32 rows and 32 columns of 1024 individual addressable amperometric cells on a 30 mm × 30 mm Si substrate consisting of Clark-type oxygen electrodes, leading to a novel real time oxygen concentration mapping, and it is important for transplantation medicine and biosensor application.[121] Furthermore, because of the short response time, an application in flow injection analysis (FIA) is possible, leading to nearly real-time multiple analyte detection if an amperometric biosensor is built up. This sensor array could be a technological base for developing a total biochemical microanalysis system.

An ultramicroelectrode array based on Ag as reference electrode and Pt as working electrode was constructed for *in vivo* blood oxygen levels assay.[122] It can also be used in a flow cell, and it has got a good response time, linearity, and reproducibility.

A microelectrode array that consisted of 10 groups of 40 Pt microelectrodes (36 μm × 36 μm) connected in parallel was coated sequentially with a membrane applied as 2 × 10 μl portion of 5% (v/v) Nafion in ethanol and a thin layer of 2.5% (v/v) PEI in methanol. This was used for glucose, L-lactate, and uric acid assay.[123] The enzymes used for sensor array design are glucose oxidase, lactate oxidase, and uricase. The calibration graphs were linear for 2.5 to 400 μmol/l H_2O_2 solution. The detection limits recorded are between 2.5 and 17.5 μmol/l.

For glucose assay, an microelectrode array based on modified immobilized glucose oxidase membrane and Nafion coating is recommended.[124] Ag/AgCl and Pt electrodes were used as reference and auxiliary electrodes. The top insulator was Si_3N_4. The linear concentration range recorded is 0.5 to 40 mmol/l, at 37°C and pH = 7.0, with a RSD of 3.4%. The sensitivity is 7.1+/–0.5 nA/ mmol/l, and the response time 3 s.

For the determination of activities of alkaline phosphatase (I) and β-galactosidase (II) using *p*-aminophenyl phosphate and *p*-aminophenyl β-D-galactopyranoside, respectively, as substrates a multiple elements analyzer (MEA) microelectrode array based on Ti, Pt, and Si in a chip is recommended.[125] The detection limits were 0.1 and 0.5 pmol/l for I and II, respectively.

Different designs of carbon thin films (4000 Å thick) were deposited onto a silicon wafer, passivated by a layer (2000 Å thick) of Si_3N_4 for dopamine assay through cyclic voltammetry technique with a detection limit of 50 nmol/l [126].

Multiple microelectrode arrays were fabricated and tested for monitoring biological cells in cultures.[127] Electrical signals were recorded extracellularly from individual neural and cardiac cells *in vitro*. The device can be adapted as multianalyte, biosensors by immobilizing a variety of biological molecules on the electrode array.

Pressure, temperature, pH, and combined O_2/CO_2 microsensors were mounted on a micromachined carrier of silicon and pyrex. The resulting array system was suitable for the analysis of biological fluids[128] *in situ* and *in vivo*.

Potentiometric microelectrode arrays are successful used for *in vivo* measurements despite their low selectivity and sensitivity.

A calcium-selective polymeric membrane microelectrode array is recommended for *in vivo* measurement of calcium in blood.[129] Low potential drift and long-term stability were exhibited by the devices. The main calibration characteristics were shown to be stable over 14 days in contact with whole blood samples.

A microelectrode array for pH and K^+ is recommended for *in vivo* determination in the beating heart.[130] The preliminary *in vivo* experiments help to determine the unique ionic conduction responsible for ventricullar fibrillation in the setting of acute regional myocardial ischemia.

The microelectrode array can be also used for the determination of the quality of food. A microelectrode array based on piezoelectric microsensor is proposed for food freshness assay.[131] The sensory behavior of five different Co^{2+}-loaded porphyrins were compared, namely, four different meso-tetraphenylporphyrines, phenyl-, *p*-nitrophenyl-, *p*-bromophenyl-, and *p*-methoxyphenyl-, and an octa-alkylporphyrin (etio-porphyrin I). The best performance was achieved with the *p*-nitrophenyl derivative. The sensor is suitable for the analysis of complex gas mixtures.

For environmental analysis, microelectrode arrays of metals were used. The following materials were used for gas microelectrode arrays design: 1wt% Pd-doped SnO_2, 6wt% Al_2O_3-doped ZnO, WO_3, and ZnO.[35] Calibration graphs were linear from 0.1 to 100 ppm CH_3SH, $(CH_3)_3N$, C_2H_5OH, and CO gases. WO_3 was the most sensitive material for detection of all four gases, while ZnO was sensitive to CH_3SH. The Al_2O_3-doped ZnO was more sensitive to CH_3SH and $(CH_3)_3N$ than for C_2H_5OH and CO. The recognition probability of the neural network was 100% for 12 gas samples (n = 5).

For *in situ* determination of heavy metals in water, microelectrode arrays are recommended. [132,133] They consist of an array of 100 mercury-plated, iridium-based microdisk electrodes coated with a 300 to 600 μm thick 1.5% agarose gel membrane. They assure a good reliability of analytical information when chronoamperometry and square wave anodic stripping voltammetry techniques are used for metals assay.

The determination of H_2O_2 in swimming pools can be reliably performed using a ultramicroelectrode array based on Si thin film.[134] It consists on nine miniaturized Pt working electrodes connected in parallel. A Pt auxiliary electrode and an Ag/AgCl reference electrode were used. The calibration graph was linear up to 422 mg/l H_2O_2 solution.

V. CONCLUSIONS

The possibility to measure direct, without any prior separation, the concentration of a component in complex matrices was assured by using sensor arrays that demonstrated the best reliability for environmental, food, and clinical analysis. The inteferences are not a problem for a sensor array due to the increase of the role of chemometrics in the data processing step. Chemometrics is the key for any sensor array development. Artificial neural networks was proven to give the best results when it is applied for sensor array signals processing.

The construction of sensor arrays must be reliable because only a reliable construction will assure reliable response characteristics and reliable analytical information. The development of electronics and chemometrics permitted the construction of a large variety of sensor arrays: ion-selective electrode arrays, gas sensor arrays, ISFET arrays, piezoelectric sensor arrays, biosensor arrays, electronic noses, and microelectrode arrays. If electronic noses have got a high importance in food analysis, microelectrode arrays have the advantages in clinical analysis due to the possibility of their applications *in vivo* assay.

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